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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/203, 9/14, 9/48 — A1

(11) International Publication Number: **WO 00/25772**

(43) International Publication Date: 11 May 2000 (11.05.00)

(21) International Application Number: PCT EP99/08208

(22) International Filing Date: 29 October 1999 (29.10.99)

(30) Priority Data:
60 106,331 30 October 1998 (30.10.98) US

(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124, Grenzacherstrasse, CH-4070 Basle (CH).

(72) Inventors: AHMED, Hashim, A.; 80 Summer Street #3, Passaic, NJ 07055 (US). INFELD, Martin, Howard; 6 Puers Place, Upper Montclair, NJ 07043 (US). SHAH, Navnit, Hargovindas; 203 Beverly Hill Road, Clifton, NJ 07012 (US).

(74) Agent: KJELLSAA-BERGER, Hanny; 124 Grenzacherstrasse, CH-4070 Basle (CH).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: COMPOSITIONS OF AND PROCESS FOR PRODUCING ISOTRETINOIN HAVING LOW PARTICLE SIZE

(57) Abstract

A process for preparing a micronized isotretinoin composition is disclosed. The process is carried out by micronizing the isotretinoin while it is suspended in an oily vehicle. Compositions of micronized isotretinoin and unit dosage forms containing the compositions are also disclosed. Certain of these compositions are superior to known compositions with respect to food effect.

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COMPOSITIONS OF AND PROCESS FOR PRODUCING ISOTRETINOIN HAVING LOW PARTICLE SIZE

The invention relates to a new process for making a micronized isotretinoin composition, specifically to a process for producing low particle size isotretinoin, to compositions comprising isotretinoin produced by this process, and to isotretinoin compositions having reduced food effect on bioavailabitily.

Isotretinoin is used for the treatment of severe, recalcitrant cystic acne. The presently marketed product ROACCUTANE® is a suspension of isotretinoin filled in soft gelatin capsules. The mean particle size of the isotretinoin in the suspension is about 90-100 μm (micrometers). This particle size is produced by subjecting a suspension of isotretinoin in an oil (preferably soybean oil) to high shear homogenization for a time sufficient to reduce the mean particle size of the isotretinoin to 90-100 μm. However, the bioavailability of the isotretinoin in ACCUTANE is only about 20%. Therefore, it was desired to reduce the particle size of isotretinoin in the suspension to improve bioavailability and also potentially reduce intra subject variability.

The reduction of isotretinoin particle size is not without problems. The particle size reduction using prior art methods, such as a hammer mill, a ball mill or an air attrition (fluid energy) mill result in a significant loss in potency of the isotretinoin. Isotretinoin is very sensitive to oxidation, and prolonged exposure to the atmosphere during milling causes substantial loss in potency. Moreover, ball milling results in contamination of the drug with the grinding media. Therefore, these approaches are not suitable for an isotretinoin commercial application.

It has been found that isotretinoin powder can be micronized with negligible loss

as defined below or wet milling; efficient particle size reduction occurs with

negligible loss in its potency. Thus one of the embodiments of the invention is an improved process for making a micronized isotretinoin composition. It was also surprisingly found that the isotretinoin composition thus produced was more storage stable with respect to isotretinoin potency than a similar composition in which the isotretinoin was first micronized and then suspended in the oil. Therefore, in accordance with the present invention, isotretinoin suspended in the oily or other pharmaceutically acceptable vehicle may be micronized by a number of techniques without a negative effect on the potency of the isotretinoin, and the suspension and soft gelatin capsules produced from this suspension exhibit excellent uniformity, bioavailability and stability of potency. Thus, further embodiments of the invention are 1) a composition comprising a suspension of isotretinoin in an oily or other pharmaceutically acceptable vehicle produced by micronizing the isotretinoin in the vehicle, and 2) a unit dosage for for enteral administration containing the composition.

The subject invention provides a pharmaceutical composition in unit dosage form. This composition comprises a suspension containing from about 7.5 mg to about 22.5 mg of isotretinoin having a mean particle size between 5 μm and 30 μm, from 10% by weight to 18% by weight of wax, preferably 18% wax, and an oil. Other useful additives in the suspension include disodium edetate and butylated hydroxyanisole. The suspension typically contains a wax mixture comprising beeswax, hydrogenated soybean oil flakes, and hydrogenated vegetable oil, and an oil, such as soybean oil. A preferred isotretinoin has a mean particle size between 5 μm and 26 μm.

As used herein, the term "liquid jet micronizer" refers to devices which utilize the micronization technology disclosed in U.S. Patent Nos. 4,533,254 and 4,908,154 the disclosures of which are hereby incorporated by reference.

The term "oily or other pharmaceutically acceptable vehicle" as used in the subject application means any liquid that is (i) pharmaceutically acceptable for oral administration into humans, (ii) of suitable fluidity and viscosity for suspending the isotretinoin while the vehicle and isotretinoin are subjected to mechanical means that produce shear, impact, cavitation or attrition so as to reduce the mean particle size of the isotretinoin to a particle size in the range of from about 5 μm to

about 30 μm, and (iii) compatible with maintaining the integrity of the capsule that is to contain the suspension. A preferred class of vehicle is an oily vehicle. An oily vehicle may be any conventional vegetable or synthetic oil pharmaceutically acceptable for oral administration. Preferred oily vehicles include soybean oil, peanut oil, olive oil, mono-, di- and triglycerides of C_6-C_{18} fatty acids, C_6-C_{18} fatty acids, polyethylene glycol, polyglycolized glycerides, glycerol, propylene glycol, mono-, di- and triesters of propylene glycol and polyethylene glycols. Mixtures of two or more oily vehicles useful in accordance with the present invention may also be used. An especially preferred oily vehicle is soybean oil.

Thus, the present invention is directed to a process for the manufacture of a micronized isotretinoin composition comprised of micronized isotretinoin dispersed in an oily or other pharmaceutically acceptable vehicle in which the micronized isotretinoin in said composition has a mean particle size in the range from about 5 μm to about 30 μm preferably from about 5 μm to about 26 μm, most preferably from about 5 μm to about 20 μm. The process comprises subjecting a suspension of isotretinoin in the oily or other pharmaceutically acceptable vehicle to mechanical means which produce shear, impact, cavitation or attrition whereby the mean particle size of the isotretinoin is reduced so as to produce the micronized isotretinoin composition. The starting isotretinoin, as distinguished from the micronized isotretinoin, generally has a mean particle size in the range from 100 μm to about 300 μm. The process of the invention may be carried out in more than one step using different mechanical means for each step, e.g., high shear homogenization followed by liquid jet micronization.

In a preferred embodiment, isotretinoin is suspended in the oily or other pharmaceutically acceptable vehicle and processed through a high shear homogenizer followed by a liquid jet micronizer. Particle size reduction using the high shear homogenizer is preferably carried out until the mean particle size of the isotretinoin in the suspension is in the range of 50-65 μm. In these two steps, the mean particle size of the isotretinoin is reduced from 100-300 μm to about 5-

The especially preferred liquid jet micronizers are those manufactured by Microfluidics Corp., Newton, MA, under the name MICROFLUIDIZER®. A recycling of the isotretinoin dispersion in the liquid jet micronizer as described in the US Patents Nos. 4 533 254 and 4 908 154 may be done, if desired, to achieve the desired size of the dispersed isotretinoin particles and/or to make them of more uniform size. In the liquid jet micronizer, the use of a larger interaction chamber in sequence with a smaller interaction chamber is preferably used.

In the preferred embodiment of the invention, the suspension from the high shear homogenizer is passed through a liquid jet micronizer at any conventional temperature at which the desired micronization may be achieved. Temperatures in the range of 15°-50°C are preferred. It is especially preferred to carry out the liquid jet micronization at room temperature. The liquid jet micronizer is preferably operated at 5,000 to 40,000 psi pressure especially at 10,000 to 30,000 psi, most preferably at 12,000 to 18,000 psi, to achieve the final particle size reduction. In a typical case, the homogenized suspension is processed twice through the liquid jet micronizer at a pressure of about 12,000 psi.

In alternative embodiments, the particle size reduction may be completed using only the high shear homogenizer for a sufficient time to yield the mean particle size of 5-30 μm especially of 5-26 μm, most preferably of 5-20 μm, or be performed using wet milling alone or liquid jet micronization alone. Examples of high shear homogenizers are impeller-type high shear mixers which may be obtained from Arde Barinco (New Jersey; e.g., Model CJ4C 16#), Koruma (Germany; e.g., Model DISHO-V), GEI Krieger (Switzerland; e.g., Model BL) and Silverson (England; e.g., Model L4 RT). Examples of wet mills are the Dispermat SL (VMA-Getzmann GMBH, Germany) and the Dyno-Mill Type KDL (Willy Bachofen AG Maschinenfabrik, Switzerland).

In a preferred embodiment of the invention, the process of the invention is carried out on a dispersion of isotretinoin in the oily or other pharmaceutically acceptable vehicle, preferably in an oily vehicule, alone or with just a conventional antioxidant, without the further excipients that might be utilized in the final formulation for filling gelatin capsules. Such a "stock dispersion" of micronized isotretinoin in the oily or other pharmaceutically acceptable vehicle is preferably used to prepare the final formulation for filling gelatin capsules. In preparation for

micronization, powdered isotretinoin may be mixed with the oily or other pharmaceutically acceptable vehicle by any conventional means. The isotretinoin in the vehicle is micronized, and then the resulting stock dispersion may be mixed with excipients to form the final formulation used for filling gelatin capsules. An example of a conventional antioxidant that might be incorporated in a stock dispersion is butylated hydroxyanisole.

One general procedure for preparing the stock dispersion is to warm the oily or other pharmaceutically acceptable vehicle to facilitate mixing (about 70°C is suitable), and dissolve the antioxidant in the vehicle using a propeller mixer or equivalent. The solution of the antioxidant in vehicle is cooled to about 35°-40° C. Isotretinoin, which is preferably stored at -20 °C in a sealed container, is brought to room temperature and the container is opened and the drug is stirred into the solution of the antioxidant in the vehicle. This dispersion of isotretinoin in the vehicle is then micronized in accordance with the process of the invention.

In the stock dispersion, the concentration (w/w) of isotretinoin in the oily vehicle is 1-50%, preferably 10-40% and most preferably 20-35%. After micronization, the stock dispersion may then be combined with additional pharmaceutically acceptable ingredients to arrive at a final formulation for filling soft gelatin capsules. An example of a stock dispersion containing 20% isotretinoin is shown in Table 1.

Table 1: Formulation of a 20% (w/w) isotretinoin stock dispersion

Ingredient	% w/w
Isotretinoin	20.0000
Butylated Hydroxyanisole (BHA)	0.0670
Soybean Oil	79.9330

The present invention is also directed to a composition in unit dosage form for enteral administration comprising the micronized isotretinoin composition of the invention and a pharmaceutically acceptable carrier. The unit dosage form contains from about 1 mg to about 50 mg of isotretinoin, preferably from about 3 to about 25 mg of isotretinoin. The oily or other pharmaceutically acceptable vehicle may, itself, act as the pharmaceutically acceptable carrier without the addition of further excipients. The unit dosage form may be any conventional form of tablet, capsule, etc. known in the art, so long as the micronized isotretinoin composition of the invention may be incorporated therein. The preferred unit dosage form is a gelatin capsule, especially a soft gelatin capsule such as those produced by R.P. Scherer North America, Inc. of Saint Petersburg, Florida. The preparation of a final formulation for filling soft gelatin capsules is described in Example 5.

Analysis of the particle size of the micronized isotretinoin is preferably based upon at least 3 samples which are taken randomly from different parts of the mixing container. Particle size analysis of the isotretinoin may be carried out using a conventional particle size analyzer (e.g., the Malvern MasterSizer™ Model X Version 2.5). The resultant micronized isotretinoin suspension should have a mean isotretinoin particle size of 5-30 μm preferably of 5-20 μm. Typical mean particle size data are presented in Table 2.

Table 2: Representative particle size data for isotretinoin following homogenization and liquid jet micronization at 12,000 psi (data are after 2 passes, and average of 3 measurements)

Processing Condition	10^{th} percentile	50^{th} percentile	90^{th} percentile
After high shear homogenization	9.5 ± 0.2 μm	58.3 ± 0.2 μm	134.0 ± 0.6 μm
After liquid jet micronization	3.2 ± 0.0 μm	14.4 ± 0.3 μm	46.8 ± 0.9 μm

It has been unexpectedly found that reducing the wax content of isotretinoin compositions having a mean particle size between 5 μm and 30 μm results in

improved absorption of isotretinoin in the absence of food. While it is known that isotretinoin containing compositions having greater than twenty-two percent (22%) wax tend to diminish the bioavailabilty of the active ingredient, no studies on isotretinoin having a mean particle size between 5 μm and 30 μm have addressed the effect of wax concentration on "food effect."

Isotretinoin is a lipophilic substance. Accordingly, administration is typically effected in the presence of food to maximize absorption of isotretinoin into the blood. It is known that individuals who take isotretinoin (mean particle size between 90 μm and 100 μm) in the absence of food show a reduction in their isotretinoin blood level as compared with individuals who take isotretinoin in the presence of food.

To test the food effect on the bioavailability of isotretinoin having a mean particle size between 5 μm and 30 μm, the following experiments were performed. The experiments demonstrate that for isotretinoin having a mean particle size between 5 μm and 30 μm, the food effect diminishes as the concentration of wax is lowered. This reduction in wax concentration correlates to a decrease in viscosity of the composition being tested. Amazingly, compositions having a wax content of about 18% (specifically 18.2%) were found to be markedly reduced food effect when compared to a composition containing 19.7% by weight of a wax mixture (disclosed in European Patent Publication No. 0 184 942, published August 8, 1990). It is believed that the reduced viscosity (185 to 600 centipoise) of isotretinoin containing compositions having between about 10% and about 18% wax will exhibit superior properties by minimizing food effect on isotretinoin bioavailablity.

Chemical assay of isotretinoin for different formulations investigated was carried out using a stability indicating method for isotretinoin where a high performance liquid chromatography procedure was used. The pump was Waters 600 E multisolvent delivery system with an autosampler of Waters WISP 717 plus, at a

Example 1

Fluid energy milling

Fluid energy (jet) mill size reduction involves acceleration of particles so that grinding occurs by particle-to-particle impact or impact against a solid surface. Fluid energy mills are used for micronization because of the high impact velocities possible as a result of particle acceleration in a fast gas stream. Particle velocities in a fluid energy mill are in the range of 300 to 500 meters per second, compared with 50 to 150 meters per second in a mechanical impact mill.

In a typical fluid energy mill process, powdered isotretinoin was fed into a mill (Jet-O-Mizer™, Fluid Energy Aljet, Plumsteadville, Pennsylvania) using a vibratory feeder which controlled the feed rate of the powder. There were three main factors which controlled the size reduction process: the powder feed rate, air pressure on the pushing nozzle (25-35 psi for a lab scale mill), and air pressure on the grinding nozzle (40-50 psi for a lab scale mill). The milling process for isotretinoin was carried out using either nitrogen or air. Samples were selected from the micronized powder and tested for potency and particle size. Results are shown in Table 3.

Example 2

Homogenization

Particle size reduction of isotretinoin was achieved using a high shear homogenizer (Model CJ4C 16#, Arde-Barinco, New Jersey). Isotretinoin was added to soybean oil (Table 1 formulation with antioxidant) and homogenized at high speed for different times (30 minutes to 6 hrs). Samples (2 g) were taken at different mixing times and tested for particle size of isotretinoin using Malvern MasterSizer Model X Version 2.5. Results are shown in Table 3. It was also found that reduction in particle size was a function of the mixing time.

Example 3

Wet milling

Particle size reduction of isotretinoin was achieved using a media milling machine (Dispermat SL, VMA-Getzmann GMBH, Germany) operated at 3000 RPM. Isotretinoin was added to soybean oil (Table 1 formulation with and without antioxidant) and homogenized at high speed using a high shear homogenizer

(Model CJ4C 16#, Arde-Barinco, New Jersey). The formed suspension was pumped through the grinding chamber of the media milling machine containing grinding glass beads. Particle size reduction occurs through both attrition and impact to produce the suspension of micronized isotretinoin. Samples (2 g each) were tested for particle size using Malvern MasterSizer Model X Version 2.5. Results are shown in Table 3.

Example 4

High shear homogenization and liquid jet micronization

Isotretinoin which was stored at -20 °C in a sealed container was brought to room temperature and was suspended in soybean oil (Table 1 formulation with and without antioxidant). The isotretinoin suspension was passed through a high shear homogenizer, as described in Example 2, until the isotretinoin particle size in the suspension was in the range of 50-65 μm. The suspension thus prepared was passed through a MICROFLUIDIZER® M110F liquid jet micronizer (Microfluidics International Corp., Newton, MA) at room temperature operated at 12,000 psi. After 2 passes, the mean particle size of the isotretinoin in the suspension was 10-20 μm. The isotretinoin particle size was determined using a Malvern MasterSizer Model X Version 2.5. Results are shown in Table 3.

The following table compares the results for fluid energy mills with various embodiments of the invention.

Table 3: Physical and chemical data for isotretinoin formulations prepared using different technologies

Example #	Processing Method	Particle size (µm)		Assay % Before Micronization	Assay % After Micronization	Assay % 3 months 40°C/75% RH	Assay % 6 months 40°C/75% RH
		d_{50}	d_{90}				
	Unprocessed isotretinoin	126.7	362.2	99.5	—	—	—
1	Fluid energy mill (air)	6.6	16.3	99.4	94.9	33.1	—
1	Fluid energy mill (N_2)	6.5	16.4	99.4	95.4	60.6	88.0*
2	Wet Milling with BHA	7.9	16.0	99.4	100.8	102.6	—
2	Wet Milling without BHA	7.9	16.0	99.4	100.2	97.5	—
3	High Shear Homogenization with BHA	12.5	41.2	99.4	100.9	99.0	—
4	High Shear Homogenization + MICROFLUIDIZER® (M110F) with BHA	11.9	39.6	99.4	101.7	100.9	
4	High Shear Homogenization + MICROFLUIDIZER® (M110F) without BHA	12.3	40.1	99.4	99.1	98.2	—
4	High Shear Homogenization + MICROFLUIDIZER® (M210EH) with BHA	12.5	29.1	99.4	100.1	99.5	98.0

* Dispersed in oil with BHA after micronization

Example 5

Preparation of Final Capsules

Table 4: Formulation of a final suspension for filling gelatin capsules

Isotretinoin Soft Gelatin Capsules Fill Composition (in mg per capsule)			
Ingredient	7.5 mg***	15 mg***	22.5 mg***
20% micronized isotretinoin stock suspension	37.5	75.0	112.5
Beeswax Purified	5.0	10.0	15.0
Hydrogenated Soybean Oil Flakes	5.0	10.0	15.0
Hydrogenated Vegetable Oil	20.0	40.0	60.0
Disodium Edetate	0.5	1.0	1.5
Butylated Hydroxyanisole (BHA)	0.1	0.2	0.3
Soybean Oil	96.9	193.8	290.7
Total	165.0	330.0	495.0

*** Final isotretinoin quantity per capsule

During the preparation of the final suspension, the vehicle (soybean oil) was warmed to about 70°C while adding the remainder of BHA and mixed using a suitable mixer until BHA was completely dissolved. Hydrogenated soybean oil flakes were added to the solution of BHA in soybean oil while mixing until it was uniformly incorporated. Subsequently, beeswax purified, hydrogenated vegetable oil and disodium edetate were added and mixing was continued to form a uniform suspension. The suspension was allowed to cool to 40° - 45°C before adding the 20% micronized isotretinoin stock dispersion, and mixing was continued until a homogeneous suspension was formed. The final suspension was blanketed with nitrogen for storage. The completed suspension was incorporated into soft gelatin capsules using conventional processing technology.

concentrations

A thirty-five percent (35%) isotretinoin stock dispersion in soybean oil was prepared

by warming the soybean oil to 70° ± 5°C and then adding BHA using a propeller mixer until the BHA was completely dissolved. The mixture was cooled to 40° - 45°C, before adding isotretinoin (under nitrogen) while mixing. The mixture was homogenized using a high shear mixer-homogenizer for 1 hour at high speed. The mixture was further passed through a wet milling machine similar to the one described in Example 3. The mean particle size (50th percentile) of isotretinoin was 20 µm. The formulation composition of the thirty-five percent (35%) isotretinoin stock dispersion in soybean oil is shown in Table 5.

Table 5: Formulation composition of the 35% stock dispersion

Item #	Ingredient	mg
1	Isotretinoin	20
2	Butylated Hydroxyanisole (BHA)	0.044
3	Soybean Oil	37.11
	Total	57.15

Using the thirty-five percent (35%) stock dispersion of isotretinoin. four (4) formulations (P1, P2, P4 and P5) were prepared with different wax concentrations [18.2%, 19.7%, 10%, and 15% (w/w), respectively]. The composition of each of the four formulations, P1, P2, P4, and P5, is shown in Tables 6,7,8 and 9, respectively.

Table 6: Formulation composition of P1

Item #	Ingredient	mg/Capsule
1	35% Stock Dispersion	57.150
2	Beeswax Purified	13.330
3	Hydrogenated Soybean Oil Flakes	13.330
4	Hydrogenated Vegetable Oil	53.330
5	Disodium Edetate	1.300
6	Butylated Hydroxyanisole (BHA)	0.222
7	Soybean Oil	301.338
Total		440.000

Table 7: Formulation composition of P2

Item #	Ingredient	mg/Capsule
1	35% Stock Dispersion	57.150
2	Wax mixture	65.000*
5	Disodium Edetate	0.990
6	Butylated Hydroxyanisole (BHA)	0.176
7	Soybean Oil	206.684
Total		330.000

* Wax mixture:

1 Part: Yellow wax (beeswax purified)

Table 8: Formulation composition of P4

Item #	Ingredient	mg/Capsule
1	35% Stock Dispersion	57.150
2	Beeswax Purified	7.330
3	Hydrogenated Soybean Oil Flakes	7.330
4	Hydrogenated Vegetable Oil	29.340
5	Disodium Edetate	1.300
6	Butylated Hydroxyanisole (BHA)	0.222
7	Soybean Oil	337.328
Total		440.000

Table 9: Formulation composition of P5

Item #	Ingredient	mg/Capsule
1	35% Stock Dispersion	57.150
2	Beeswax Purified	11.000
3	Hydrogenated Soybean Oil Flakes	11.000
4	Hydrogenated Vegetable Oil	44.000
5	Disodium Edetate	1.300
6	Butylated Hydroxyanisole (BHA)	0.222
7	Soybean Oil	315.328
Total		440.000

For formulations P1, P4 and P5, during the preparation of the final suspension, the vehicle (soybean oil) was warmed to about 70°C while adding the remainder of BHA and mixed using a suitable mixer until BHA was completely dissolved.

Hydrogenated soybean oil flakes was added to the solution of BHA in soybean oil while mixing until it was uniformly incorporated. Subsequently, beeswax purified, hydrogenated vegetable oil and disodium edetate were added. Mixing was continued to form a uniform suspension. The suspension was allowed to cool to 40° - 45°C before adding the 35% stock dispersion of isotretinoin, and mixing was continued until a homogeneous suspension was formed. The final suspension was blanketed with nitrogen for storage. The completed suspension was manually incorporated into hard gelatin capsules.

Formulation P2 (disclosed in European Patent Publication No. 0 184 942, published August 8, 1990) was prepared in a manner similar to the other three (3) formulations. However a wax mixture (the composition of which is described with Table 7) was prepared first before addition to the warmed soybean oil in accordance with the published European Patent Publication. After addition of the wax mixture, the processing continued as for the other three (3) formulations, i.e. P1, P4, and P5.

The viscosity of all formulations was measured at 25°C using a Brookfield Digital Viscometer Model DV-II equipped with Brookfield Small Sample Adapter Model SSA-15/7R using spindle # 15 set at 100 rpm Knob speed. Viscosity data for all four (4) formulations are shown on Table 10.

The four (4) formulations were orally administered to fed and fasted dogs to compare the effect on plasma exposure. Six (6) male and six (6) female dogs were placed into two (2) groups of three (3) males and three (3) females according to a standard randomization procedure. The 4 formulations (P1, P2, P4 and P5) were administered to each dog at 20 mg isotretinoin per dog under fed and fasted conditions. Blood samples were collected from all dogs into tubes containing potassium oxalate and sodium fluoride as anticoagulant, and placed over ice prior to centrifugation. Samples were taken prior to dosing and 1 hr, 2 hrs, 3 hrs, 4 hrs, 6 hrs, 8 hrs, 10 hrs, 12 hrs, 24 hrs, 28 hrs and 32 hrs after dosing. Plasma was separated [illegible] frozen in amber vials at a minimum of -

Watson (v 5.4.00.03) validated laboratory information system. The pharmacokinetic parameters were estimated from the individual data. The parameters reported are

the maximum plasma concentration (C_{max}), the time to reach the maximum plasma concentration (T_{max}), and the area under the plasma concentration-time curve from zero to 32 hours ($AUC_{0-32\ hr}$). The observed C_{max} and T_{max} were taken directly from the individual plasma concentration-time profiles. The $AUC_{0-32\ hr}$ was calculated using the linear trapezoidal rule. The mean pharmacokinetic data are shown in Table 10.

Table 10: Mean pharmacokinetics data for different formulations investigated following testing in fed and fasted dogs

Formulation	ntent (% w/w)	Viscosity (cps)	Fasted Dogs		Fed Dogs		$AUC_{0\text{-}32\ hr}$ Fed/Fasted Ratio
			C_{max} (ng/mL)	AUC (ng*h/mL)	C_{max} (ng/mL)	AUC (ng*h/mL)	
		505	1190 ± 266	4800 ± 192	978 ± 308	6500 ± 1310	1.35
		1270	903 ± 468	3580 ± 855	983 ± 204	6420 ± 556	1.79
		185	1240 ± 570	4970 ± 2040	1170 ± 356	7580 ± 2460	1.53
		315	755 ± 273	3650 ± 1550	1110 ± 288	6560 ± 2160	1.80

Upon reading this specification various alternative embodiments will become obvious to the skilled artisan. These variations are to be considered within the scope and spirit of the subject invention which is only to be limited by the claims that follow and their equivalents.

Claims

1. A process for the manufacture of a micronized isotretinoin composition, the composition comprising isotretinoin having a mean particle size in the range from about 5 μm to about 30 μm suspended in an oily or other pharmaceutically acceptable vehicle, wherein the process comprises:

1) dispersing isotretinoin having a mean particle size greater than about 30 μm in the vehicle to form a suspension containing 1-50% by weight of isotretinoin;

2) subjecting the suspension to mechanical means which produce shear, impact, cavitation or attrition so as to reduce the mean particle size of the isotretinoin to a particle size in the range from about 5 μm to about 30 μm;

whereby the micronized isotretinoin composition is produced.

2. The process of claim 1, wherein the mechanical means is wet milling.

3. The process of claim 2, wherein the suspension contains from 10-40% by weight of isotretinoin.

4. The process of claim 3, wherein the suspension contains from 20-35% by weight of isotretinoin.

5. The process of claim 2, wherein the vehicle is an oily vehicle.

6. The process of claim 5, wherein the oily vehicle comprises soybean oil, peanut oil, olive oil, a mono-, di- or triglyceride of a C_6-C_{18} fatty acid, C_6-C_{18} fatty acid, polyethylene glycol, a polyglycolized glyceride, glycerol, propylene glycol, a mono-, di- or triester of propylene glycol, or a polyethylene glycol.

7. The process of claim 6, wherein the oily vehicle is soybean oil.

9. The process of claim 8, wherein the suspension contains from 10-40% by weight of isotretinoin.

10. The process of claim 9, wherein the suspension contains from 20-35% by weight of isotretinoin.

11. The process of claim 8, wherein the vehicle is an oily vehicle.

12. The process of claim 11, wherein the oily vehicle comprises soybean oil, peanut oil, olive oil, a mono-, di- or triglyceride of a C_6-C_{18} fatty acid, polyethylene glycol, a polyglycolized glyceride, glycerol, propylene glycol, a mono-, di- or triester of propylene glycol, or a polyethylene glycol.

13. The process of claim 12, wherein the oily vehicle is soybean oil.

14. The process of claim 1, wherein the mechanical means is liquid jet micronization.

15. The process of claim 14, wherein the suspension contains from 10-40% by weight of isotretinoin.

16. The process of claim 15, wherein the suspension contains from 20-35% by weight of isotretinoin.

17. The process of claim 14, wherein the vehicle is an oily vehicle.

18. The process of claim 17, wherein the oily vehicle comprises soybean oil, peanut oil, olive oil, a mono-, di- or triglyceride of a C_6-C_{18} fatty acid, C_6-C_{18} fatty acid, polyethylene glycol, a polyglycolized glyceride, glycerol, propylene glycol, a mono-, di- or triester of propylene glycol, or a polyethylene glycol.

19. The process of claim 18, wherein the oily vehicle is soybean oil.

20. The process of claim 1, wherein the mechanical means is high shear homogenization followed by liquid jet micronization.

21. The process of claim 20, wherein the suspension contains from 10-40% by weight of isotretinoin.

22. The process of claim 21, wherein the suspension contains from 20-35% by weight of isotretinoin.

23. The process of claim 20, wherein the vehicle is an oily vehicle.

24. The process of claim 23, wherein the oily vehicle comprises soybean oil, peanut oil, olive oil, a mono-, di- or triglyceride of a C_6-C_{18} fatty acid, C_6-C_{18} fatty acid, polyethylene glycol, a polyglycolized glyceride, glycerol, propylene glycol, a mono-, di- or triester of propylene glycol, or a polyethylene glycol.

25. The process of claim 24, wherein the mean particle size of the isotretinoin in the suspension is in the range from about 50 μm to about 65 μm after the high shear homogenization.

26. The process of claim 24, wherein the oily vehicle is soybean oil.

27. A micronized isotretinoin composition, the composition comprising isotretinoin having a mean particle size in the range from about 5 μm to about 30 μm suspended in an oily or other pharmaceutically acceptable vehicle, wherein the composition is made by a process which comprises:

1) dispersing isotretinoin having a mean particle size greater than about 30 μm in the vehicle to form a suspension containing 1-50% by weight of isotretinoin;

2) subjecting the suspension to mechanical means which produce shear, impact, cavitation or attrition so as to reduce the mean particle size of the isotretinoin to a particle size in the range from about 5 μm to about 30 μm;

whereby the micronized isotretinoin composition is produced.

28. The composition of claim 27, wherein the mechanical means is wet milling.

29. The composition of claim 28, wherein the suspension contains from 10-40% by

30. The composition of claim 29, wherein the suspension contains from 20-35% by weight of isotretinoin.

31. The composition of claim 27, wherein the vehicle is an oily vehicle.

32. The composition of claim 31, wherein the oily vehicle comprises soybean oil, peanut oil, olive oil, a mono-, di- or triglyceride of a C_6-C_{18} fatty acid, C_6-C_{18} fatty acid, polyethylene glycol, a polyglycolized glyceride, glycerol, propylene glycol, a mono-, di- or triester of propylene glycol, or a polyethylene glycol.

33. The composition of claim 32, wherein the oily vehicle is soybean oil.

34. The composition of claim 27, wherein the mechanical means is high shear homogenization.

35. The composition of claim 34, wherein the suspension contains from 10-40% by weight of isotretinoin.

36. The composition of claim 35, wherein the suspension contains from 20-35% by weight of isotretinoin.

37. The composition of claim 34, wherein the vehicle is an oily vehicle.

38. The composition of claim 37, wherein the oily vehicle comprises soybean oil, peanut oil, olive oil, a mono-, di- or triglyceride of a C_6-C_{18} fatty acid, C_6-C_{18} fatty acid, polyethylene glycol, a polyglycolized glyceride, glycerol, propylene glycol, a mono-, di- or triester of propylene glycol, or a polyethylene glycol.

39. The composition of claim 38, wherein the oily vehicle is soybean oil.

40. The composition of claim 27, wherein the mechanical means is liquid jet micronization.

41. The composition of claim 40, wherein the suspension contains from 10-40% by weight of isotretinoin.

42. The composition of claim 41, wherein the suspension contains from 20-35% by weight of isotretinoin.

43. The composition of claim 40, wherein the vehicle is an oily vehicle.

44. The composition of claim 43, wherein the oily vehicle comprises soybean oil, peanut oil, olive oil, a mono-, di- or triglyceride of a C_6-C_{18} fatty acid, C_6-C_{18} fatty acid, polyethylene glycol, a polyglycolized glyceride, glycerol, propylene glycol, a mono-, di- or triester of propylene glycol, or a polyethylene glycol.

45. The composition of claim 44, wherein the oily vehicle is soybean oil.

46. The composition of claim 27, wherein the mechanical means is high shear homogenization followed by liquid jet micronization.

47. The composition of claim 46, wherein the suspension contains from 10-40% by weight of isotretinoin.

48. The composition of claim 47, wherein the suspension contains from 20-35% by weight of isotretinoin.

49. The composition of claim 46, wherein the vehicle is an oily vehicle.

50. The composition of claim 49, wherein the oily vehicle comprises soybean oil, peanut oil, olive oil, a mono-, di- or triglyceride of a C_6-C_{18} fatty acid, C_6-C_{18} fatty acid, polyethylene glycol, a polyglycolized glyceride, glycerol, propylene glycol, a mono-, di- or triester of propylene glycol, or a polyethylene glycol.

51. The composition of claim 50, wherein the mean particle size of the isotretinoin in the suspension is in the range from about 50 μm to about 65 μm after the high shear homogenization.

52. The composition of claim 50, wherein the oily vehicle is soybean oil.

53. A unit dosage form for enteral administration containing a micronized isotretinoin composition, the composition comprising isotretinoin having a mean particle size in the range from about 5 μm to about 30 μm suspended in an oily or

1) dispersing isotretinoin having a mean particle size greater than about 30 μm in the oily vehicle to form a suspension containing 1-50% by weight of isotretinoin;

2) subjecting the suspension to mechanical means which produce shear, impact, cavitation or attrition so as to reduce the mean particle size of the isotretinoin to a particle size in the range from about 5 μm to about 30 μm;

whereby the micronized isotretinoin composition is produced;

wherein the unit dosage form contains from about 1 mg to about 50 mg of isotretinoin.

54. The unit dosage form of claim 53, wherein the unit dosage form contains from about 3 mg to about 25 mg of isotretinoin.

55. The unit dosage form of claim 53, wherein the mechanical means is wet milling.

56. The unit dosage form of claim 55, wherein the suspension contains from 10-40% by weight of isotretinoin.

57. The unit dosage form of claim 56, wherein the suspension contains from 20-35% by weight of isotretinoin.

58. The unit dosage form of claim 55, wherein the vehicle is an oily vehicle.

59. The unit dosage form of claim 58, wherein the oily vehicle comprises soybean oil, peanut oil, olive oil, a mono-, di- or triglyceride of a C_6-C_{18} fatty acid, C_6-C_{18} fatty acid, polyethylene glycol, a polyglycolized glyceride, glycerol, propylene glycol, a mono-, di- or triester of propylene glycol, or a polyethylene glycol.

60. The unit dosage form of claim 59, wherein the unit dosage form is a capsule.

61. The unit dosage form of claim 60, wherein the capsule is a soft gelatin capsule.

62. The unit dosage form of claim 59, wherein the oily vehicle is soybean oil.

63. The unit dosage form of claim 53, wherein the mechanical means is high shear homogenization.

64. The unit dosage form of claim 63, wherein the suspension contains from 10-40% by weight of isotretinoin.

65. The unit dosage form of claim 64, wherein the suspension contains from 20-35% by weight of isotretinoin.

66. The unit dosage form of claim 63, wherein the vehicle is an oily vehicle.

67. The unit dosage form of claim 66, wherein the oily vehicle comprises soybean oil, peanut oil, olive oil, a mono-, di- or triglyceride of a C_6-C_{18} fatty acid, C_6-C_{18} fatty acid, polyethylene glycol, a polyglycolized glyceride, glycerol, propylene glycol, a mono-, di- or triester of propylene glycol, or a polyethylene glycol.

68. The unit dosage form of claim 67, wherein the unit dosage form is a capsule.

69. The unit dosage form of claim 68, wherein the capsule is a soft gelatin capsule.

70. The unit dosage form of claim 67, wherein the oily vehicle is soybean oil.

71. The unit dosage form of claim 53, wherein the mechanical means is liquid jet micronization.

72. The unit dosage form of claim 71, wherein the suspension contains from 10-40% by weight of isotretinoin.

73. The unit dosage form of claim 72, wherein the suspension contains from 20-35% by weight of isotretinoin.

74. The unit dosage form of claim 71, wherein the vehicle is an oily vehicle.

75. The unit dosage form of claim 74, wherein the oily vehicle comprises soybean

76. The unit dosage form of claim 75, wherein the unit dosage form is a capsule.

77. The unit dosage form of claim 76, wherein the capsule is a soft gelatin capsule.

78. The unit dosage form of claim 75, wherein the oily vehicle is soybean oil.

79. The unit dosage form of claim 53, wherein the mechanical means is high shear homogenization followed by liquid jet micronization.

80. The unit dosage form of claim 79, wherein the suspension contains from 10-40% by weight of isotretinoin.

81. The unit dosage form of claim 80, wherein the suspension contains from 20-35% by weight of isotretinoin.

82. The unit dosage form of claim 79, wherein the vehicle is an oily vehicle.

83. The unit dosage form of claim 82, wherein the oily vehicle comprises soybean oil, peanut oil, olive oil, a mono-, di- or triglyceride of a C_6-C_{18} fatty acid, C_6-C_{18} fatty acid, polyethylene glycol, a polyglycolized glyceride, glycerol, propylene glycol, a mono-, di- or triester of propylene glycol, or a polyethylene glycol.

84. The unit dosage form of claim 83, wherein the unit dosage form is a capsule.

85. The unit dosage form of claim 84, wherein the capsule is a soft gelatin capsule.

86. The unit dosage form of claim 85, wherein the mean particle size of the isotretinoin in the suspension is in the range from about 50 µm to about 65 µm after the high shear homogenization.

87. The unit dosage form of claim 83, wherein the oily vehicle is soybean oil.

88. A pharmaceutical composition in unit dosage form, which comprises a suspension containing from about 7.5 mg to about 22.5 mg of isotretinoin having a mean particle size between 5 µm and 30 µm, about 18% by weight of wax, and an oil.

89. The composition of claim 88, wherein the suspension contains about 18.2% by weight of wax.

90. The composition of claim 88, wherein the suspension contains disodium edetate.

91. The composition of claim 88, wherein the suspension contains butylated hydroxyanisole.

92. The composition of claim 88, wherein the suspension contains a wax comprising beeswax, hydrogenated soybean oil flakes, and hydrogenated vegetable oil.

93. The composition of claim 88, wherein the suspension contains an oil which is soybean oil.

94. The composition of claim 88 which consists essentially of 7.5 mg of isotretinoin, 5 mg of beeswax, 5 mg of hydrogenated soybean oil flakes, 20 mg of hydrogenated vegetable oil, 0.5 mg of disodium edetate, 0.1 mg of butylated hydroxyanisole, and 126.9 mg of soybean oil.

95. The composition of claim 94, wherein the isotretinoin has a mean particle size between 5 μm and 26 μm, inclusive.

96. The composition of claim 88 which consists essentially of 15 mg of isotretinoin, 10 mg of beeswax, 10 mg of hydrogenated soybean oil flakes, 40 mg of hydrogenated vegetable oil, 1.0 mg of disodium edetate, 0.2 mg of butylated hydroxyanisole, and 253.8 mg of soybean oil.

97. The composition of claim 96, wherein the isotretinoin has a mean particle size between 5 μm and 26 μm, inclusive.

98. The composition of claim 88 which consists essentially of 22.5 mg of isotretinoin, 15 mg of beeswax, 15 mg of hydrogenated soybean oil flakes, 60 mg of hydrogenated vegetable oil, 1.5 mg of disodium edetate, 0.3 mg of butylated hydroxyanisole, and 380.7 of soybean oil.

99. The composition of claim 98, wherein the isotretinoin has a mean particle size

101. The composition of claim 100, wherein the unit dosage form is a soft gelatin capsule.

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INTERNATIONAL SEARCH REPORT

in ...al Application No
PCT/EP 99/08208

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/203 A61K9/14 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	GB 1 527 638 A (BAYER AG) 4 October 1978 (1978-10-04) page 3, line 1-6 page 3; example 1 claims 12-15	1-26
A	EP 0 065 193 A (BASF AG) 24 November 1982 (1982-11-24) abstract page 4, line 19 - line 29 claims 1,4,5	1-26
A	EP 0 184 942 A (ORTHO PHARMA CORP) 18 June 1986 (1986-06-18) cited in the application page 11 -page 12; examples 1-4	27-101

☐ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex

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Date of the actual completion of the international search
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/08208

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